amendments were purely grammatical. It is also believed that the amendments in do not narrow the scope of the claims.

Claim 31 has been amended to more properly recite a "truncated toxin moiety." Support for this amendment can be found throughout the application and at least on page 13, line 13-16.

35 U.S.C. § 103

The Examiner has maintained the rejection of all pending claims under 35 U.S.C. § 103, as allegedly obvious based on Chaudhary et al., Neville et al., Hirsch et al., and Whitlow et al., and, optionally, further in view of Youle *et al.* Applicants respectfully traverse the rejection.

In the June 13, 2002, Advisory Action, in response to the declaration submitted by the applicants under 37 CFR 1.132, the Examiner states, "the references [supplied with the declaration as exhibits A and B] at best, are neutral regarding the instant invention, and at worst, actually teach away from the invention." The Examiner then asserts that the references teach that "the best monovalent single claim immunotoxins are not particularly effective" and that "divalent immunotoxins are preferred." Applicants respectfully point out that the point at issue is not whether a divalent immunotoxin in hindsight is preferred, but whether the claimed immunotoxin itself has surprising and unexpected properties over the prior art (*In re Dance*, 160 F.3d 1339, 1343 (Fed. Cir. 1998)). That a divalent antibody allegedly works better than a monovalent is irrelevant as the references regarding divalent immunotoxins postdate the

invention. What is important is that the features of the claimed constructs are surprising and unexpected over the prior art. In the declaration submitted May 7, 2002, Applicants noted that one such feature of DT390 sFv(UCHT1) is that DT390 sFv(UCHT1) has greater potency relative to other immunotoxins in which the UCHT1 has been substituted for other anti-CD3 antibodies (e.g., FN18, SP34, and CHRIS-7). This is surprising because all of these construct have similar binding affinities to the target. This surprising feature is further demonstrated by Thompson et al., which shows the sFV-DT390 utilizing UCHT1 had similar toxicity to the parental antibody despite a 2-log reduction in binding affinity. This feature is in stark contrast to the results using FN18 (Ma et al.). In the case of NF18, as with the UCHT1 construct, there is a 2-log reduction in affinity; however, unlike the UCHT1 contruct, there is also a corresponding decrease in toxicity with the FN18 construct. Thus, it is surprising and unexpected that a similar construct varying only in the anti-CD3 antibody (SFvDT390-UCHT1) would show increased toxicity without a concomitant change in relative affinity.

In the Declaration attached hereto as Appendix B, Dr. Neville provides additional data that proves the relative unpredictability of the properties of imunotoxin fusion proteins. The single chain variable regions of various CD3 antibodies in immunotoxin contructs resulted in substantially different toxicities (paragraph 3), despite comparable affinities in the parental antibodies (paragraph 4). It was only by constructing the immunotoxin fusion protein and assessing its function that one skilled in the art can ascertain how effective a specific immunotoxin fusion protein was. Given the unpredictability of the art, at the time the claimed

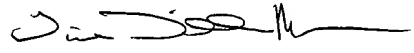
immunotoxin was made, one skilled in the art certainly could not have predicted which specific fusion immunotoxin would be vastly superior in T cell depletion. It was only through trial and error that the inventors, or others skilled in the art, could have determined that the claimed imunotoxin fusion protein was vastly superior.

Applicants respectfully request that the amendments be entered and the remarks considered. Pursuant to these amendments and remarks, reconsideration and allowance of the pending application is believed to be warranted. The PTO is invited and encouraged to directly contact the undersigned if such contact may enhance the efficient prosecution of the application to issue.

Payment in the amount of $2720.00, ($750.00 for the Request for Continued Examination and $1970.00 for the 5-month extension of time) is to be charged to a credit card and such payment is authorized by the signed, enclosed document entitled: Credit Card Payment Form PTO-2038. This amount is believed to be correct; however, the Commissioner is hereby authorized to charge any additional fees that may be required to Deposit Account No. 14-0629.

Respectfully submitted,

NEEDLE & ROSENBERG, P.C.



Tina Williams McKeon, Ph.D.
Registration No. 43,791

NEEDLE & ROSENBERG, P.C.
Suite 1200, The Candler Building
127 Peachtree Street, N.E.
Atlanta, Georgia 30303-1811
404/688-0770

I hereby certify that this correspondence as well as anything indicated as being attached or enclosed is being deposited with the United States Postal Service as Express Mail envelope EL 924 195 907US addressed to: Box RCE, Commissioner for Patents, Washington, D.C. 20231, on the date shown below.

Michael Laird

2/14/03
Date

APPENDIX A
MARKED-UP VERSION OF THE AMENDED CLAIMS

30. A fusion immunotoxin comprising a single-chain variable region of an anti-CD3 antibody linked to a toxin moiety, wherein the anti-CD3 antibody is UCHT1 and wherein the diphtheria toxin moiety is a truncation of native diphtheria toxin at the carboxy terminus.

31. The fusion immunotoxin according to claim 30, wherein the truncated toxin moiety is DT390.

32. The fusion immunotoxin according to claim 31, comprising DT390 linked via its carboxy terminus, optionally via a linker, to the single-chain variable region of the anti-CD3 antibody.

33. The fusion immunotoxin according to claim 32, wherein the single-chain variable region of the anti-CD3 antibody comprises the variable light domain linked via its carboxy terminus to the variable heavy domain, optionally via a linker.

38. A method for inhibiting rejection of transplanted tissue or organs in a subject, comprising administering to [a] the subject [in need thereof] an immunotoxin according to claim 30.

39. A method for treating a subject with an autoimmune disease, comprising administering to [a] the subject [in need thereof] an immunotoxin according to claim 30.

40. A method of treating T cell leukemias or lymphomas in a subject, comprising administering to [a] the subject [in need thereof] an immunotoxin according to claim 30.

41. A method of treating graft-versus-host disease in a subject, comprising administering to [a] the subject [in need thereof] an immunotoxin according to claim 30.

42. A method of treating acquired immunodeficiency syndrome in a subject, comprising administering to [a] the subject [in need thereof] an immunotoxin according to claim 30.